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## **CLAIMS**

## What is claimed is:

- A method of screening for an agent that modulates the uptake of glutamate into a cell, said method comprising:
- i) contacting a cell comprising a nucleic acid selected from the group consisting of VGLUT1, VGLUT2, and VGLUT3 with a test agent; and
- ii) detecting expression or activity of VGLUT1, VGLUT2, or VGLUT3 where an increase or decrease in the expression or activity of VGLUT1, VGLUT2, or VGLUT3 as compared to a control indicates that said test agent modulates the uptake of glutamate into a synaptic vesicle.
- 2. The method of claim 1, wherein said control is a negative control comprising contacting a cell at a lower concentration of said test agent.
- 3. The method of claim 2, wherein said lower concentration is the absence of said test agent.
  - 4. The method of claim 1, wherein said cell is a somatic cell.
  - 5. The method of claim 1, wherein said cell is an oocyte.
  - 6. The method of claim 1, wherein said cell is a nerve cell.
  - 7. The method of claim 1, wherein said cell is a vertebrate cell.
  - 8. The method of claim 7, wherein said cell is a mammalian cell.
  - 9. The method of claim 7, wherein said cell is a human cell.
- 10. The method of claim 1, wherein said detecting comprises detecting a VGLUT1 nucleic acid, a VGLUT2 nucleic acid, or a VGLUT3 nucleic acid.
- 11. The method of claim 1, wherein said detecting comprises detecting a VGLUT1 polypeptide, a VGLUT2 polypeptide, or a VGLUT3 polypeptide.

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- 12. The method of claim 1, wherein said detecting comprises measuring activity of a VGLUT1 polypeptide, a VGLUT2 polypeptide, or a VGLUT3 polypeptide.
- 13. The method of claim 10, wherein said detecting a VGLUT1 nucleic acid, a VGLUT2 nucleic acid or a VGLUT3 nucleic acid comprises a nucleic acid hybridization.
- 14. The method of claim 10, wherein said detecting a VGLUT1 nucleic acid, a VGLUT2 nucleic acid or a VGLUT3 nucleic acid comprises a method selected from the group consisting of a Northern blot, a Southern blot using DNA derived from the VGLUT1, VGLUT2, or VGLUT3 mRNA, an array hybridization, an affinity chromatography, and an in situ hybridization.
- 15. The method of claim 10, wherein said detecting a VGLUT1 nucleic acid, a VGLUT2 nucleic acid or a VGLUT3 nucleic acid comprises a nucleic acid amplification.
- 16. The method of claim 11, wherein said detecting a VGLUT1 polypeptide, a VGLUT2 polypeptide, or a VGLUT3 polypeptide comprises a method selected from the group consisting of capillary electrophoresis, Western blot, mass spectroscopy, ELISA, immunochromatography, thin layer chromatography, and immunohistochemistry.
- 17. The method of claim 12, wherein said measuring activity of a
  20 VGLUT1 polypeptide, a VGLUT2 polypeptide or a VGLUT3 polypeptide comprises
  detecting glutamate transport in a cell expressing a heterologous VGLUT1 polypeptide,
  VGLUT2 polypeptide or a VGLUT3 polypeptide.
  - 18. The method of claim 1, wherein said test agent is not an antibody.
  - 19. The method of claim 1, wherein said test agent is not a nucleic acid.
  - 20. The method of claim 1, wherein said test agent is not a protein.
  - 21. The method of claim 1, wherein said test agent is a small organic molecule.

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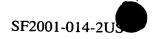
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- The method of claim 1, wherein said agent is not an agent that alters  $\Delta p H$  or  $\Delta \Psi.$
- 23. The method of claim 1, further comprising comparing the level of expression or activity of VGLUT1 with the level of expression or activity of VGLUT2 or VGLUT3.
- 24. A method of prescreening for a potential modulator of glutamate transporter activity, said method comprising:

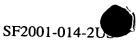
contacting a VGLUT glutamate transporter polypeptide or a nucleic acid encoding a VGLUT glutamate transporter polypeptide with a test agent; and detecting binding of said test agent to said VGLUT glutamate transporter polypeptide or to said nucleic acid encoding a VGLUT glutamate transporter polypeptide wherein specific binding of said test agent to the VGLUT glutamate transporter polypeptide or VGLUT nucleic acid indicates that said test agent is a potential modulator of glutamate transporter activity.

- 25. The method of claim 24, further comprising recording test agents that specifically bind to said VGLUT glutamate transporter polypeptide or to said nucleic acid encoding a VGLUT glutamate transporter polypeptide in a database of candidate modulators of glutamate transporter activity.
- 26. The method of claim 24, wherein said VGLUT glutamate transporter polypeptide or to said nucleic acid encoding a VGLUT glutamate transporter is a VGLUT1 polypeptide or a nucleic acid encoding a VGLUT1 polypeptide.
- 27. The method of claim 24, wherein said VGLUT glutamate transporter polypeptide or to said nucleic acid encoding a VGLUT glutamate transporter is a VGLUT2 polypeptide or a nucleic acid encoding a VGLUT2 polypeptide.
- 28. The method of claim 24, wherein said VGLUT glutamate transporter polypeptide or to said nucleic acid encoding a VGLUT glutamate transporter is a VGLUT3 polypeptide or a nucleic acid encoding a VGLUT3 polypeptide.
  - 29. The method of claim 24, wherein said test agent is not an antibody.

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- 30. The method of claim 24, wherein said test agent is not a protein.
- 31. The method of claim 24, wherein said detecting comprises detecting specific binding of said test agent to said nucleic acid encoding a VGLUT glutamate transporter polypeptide.
- The method of claim 31, wherein said binding is detected using a method selected from the group consisting of a Northern blot, a Southern blot using DNA derived from the VGLUT1, VGLUT2, or VGLUT3 mRNA, an array hybridization, an affinity chromatography, and an *in situ* hybridization.
  - 33. The method of claim 24, wherein said detecting comprises detecting specific binding of said test agent to said VGLUT glutamate transporter polypeptide.
  - 34. The method of claim 45, wherein said detecting is via a method selected from the group consisting of capillary electrophoresis, a Western blot, mass spectroscopy, ELISA, immunochromatography, thin layer chromatography, and immunohistochemistry.
  - 35. The method of claim 24, wherein said test agent is contacted directly to said VGLUT glutamate transporter polypeptide or to said nucleic acid encoding a VGLUT glutamate transporter polypeptide.
  - 36. The method of claim 24, wherein said test agent is contacted to a cell containing said VGLUT glutamate transporter polypeptide or to said nucleic acid encoding a VGLUT glutamate transporter polypeptide.
    - 37. The method of claim 36, wherein said cell is cultured ex vivo.
  - 38. A cell comprising a heterologous nucleic acid encoding a glutamate transporter wherein said glutamate transporter is selected from the group consisting of VGLUT1, VGLUT2, and VGLUT3.
- 25 39. The cell of claim 38, wherein said cell is a mammalian cell.
  - 40. The cell of claim 38, wherein said cell is a somatic cell.



- The cell of claim 38, wherein said cell is an oocyte or a nerve cell. 41.
- The cell of claim 38, wherein said cell transports glutamate via said 42. glutamate transporter.
- The cell of claim 38, wherein said cell is a pheochromocytoma PC12 43. cell.
  - 44. A method of increasing glutamate transport by a mammalian cell, said method comprising transfecting said cell with a nucleic acid encoding a VGLUT polypeptide selected from the group consisting of VGLUT1, VGLUT2, and VGLUT3.
- 45. The method of claim 44, wherein said nucleic acid encoding a VGLUT polypeptide is operably linked to a constitutive promoter.
- 46. The method of claim 44, wherein said nucleic acid encoding a VGLUT polypeptide is operably linked to an inducible promoter.
- 47. The method of claim 44, wherein said nucleic acid encoding a VGLUT polypeptide is operably linked to a tissue-specific promoter.
- 48. A kit for screening for compounds that modulate glutamate transport, said kit comprising

a cell that expresses a VGLUT glutamate transporter selected from the group consisting of VGLUT1, VGLUT2, and VGLUT3; and

- a detection moiety selected from the group consisting of an antibody that specifically binds to said VGLUT glutamate transporter, a nucleic acid that specifically 20 binds to a nucleic acid encoding said VGLUT glutamate transporter, a primer that specifically amplifies a nucleic acid encoding said VGLUT glutamate transporter or a fragment thereof, and a labeled glutamate.
- 49. The kit of claim 48, wherein said cell is cell comprising a heterologous nucleic acid encoding said glutamate transporter 25

- 50. The kit of claim 48, further comprising instructional materials providing protocols for screening for modulators of a VGLUT glutamate transporter and teaching that such modulators alter glutamate transport.
- 51. A knockout mammal, said mammal comprising a disruption in an endogenous glutamate transporter gene selected from the group consisting of *VGLUT1*, *VGLUT2*, and *VGLUT3*, wherein said disruption results in said knockout mammal exhibiting decreased expression of a VGLUT glutamate transporter as compared to a wild-type animal.
  - 52. The mammal of claim 51, wherein the mammal is selected from the group consisting of an equine, a bovine, a rodent, a porcine, a lagomorph, a feline, a canine, a murine, a caprine, an ovine, and a non-human primate.
  - 53. The mammal of claim 51, wherein the disruption is selected from the group consisting of an insertion, a deletion, a frameshift mutation, a substitution, and a stop codon.
  - 54. The mammal of claim 51, wherein the disruption comprises an insertion of an expression cassette into said endogenous glutamate transporter gene.
  - 55. The mammal of claim 54, wherein said expression cassette comprises a selectable marker.
- 56. The mammal of claim 54, wherein the expression cassette comprises a neomycin phosphotransferase gene operably linked to at least one regulatory element.
  - 57. The mammal of claim 52, wherein said disruption is in a somatic cell.
  - 58. The mammal of claim 52, wherein said disruption is in a germ cell.
  - 59. The mammal of claim 52, wherein the mammal is homozygous for the disrupted glutamate transporter gene.
- 25 60. The mammal of claim 52, wherein the mammal is heterozygous for the disrupted glutamate transporter gene.

- 61. A method of inhibiting glutamate uptake into a cell, said method comprising contacting said cell with an agent that inhibits expression or activity of a VGLUT polypeptide.
- The method of claim 53, wherein said agent is not an agent that alters  $\Delta pH$  or  $\Delta \Psi$ .
  - 63. The method of claim 53, wherein said agent is selected from the group consisting of a VGLUT antisense molecule, a VGLUT ribozyme, a VGLUT catalytic DNA, an anti-VGLUT antibody, and a nucleic acid that disrupts a VGLUT gene by homologous recombination.
  - 64. A method of increasing glutamate uptake into a cell, said method comprising contacting said cell with an agent that increases VGLUT glutamate transporter expression or activity.
  - 65. A method of inhibiting glutamate uptake into a cell, said method comprising downregulating expression or activity of a VGLUT polypeptide in said cell.
  - 66. The method of claim 65, wherein said inhibiting comprises a method selected from the group consisting of contacting a VGLUT nucleic acid with a ribozyme that specifically cleaves said VGLUT nucleic acid, contacting a VGLUT nucleic acid with a catalytic DNA that specifically cleaves said VGLUT nucleic acid, transfecting a cell comprising an VGLUT gene with a nucleic acid that inactivates the VGLUT gene by homologous recombination with the VGLUT gene, transfecting a cell comprising a with a nucleic acid encoding an intrabody that specifically binds a VGLUT polypeptide, and transfecting said cell with a VGLUT antisense molecule.

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